

Claims

1. A trimeric polypeptide comprising three monomers, each of said monomers comprising a specific binding member capable of binding a trimeric cytokine, and each of said monomers comprising a trimerising domain.
2. A trimeric polypeptide according to claim 1, wherein the trimeric cytokine is a member of the Tumor necrosis factor ligand superfamily.
3. A trimeric polypeptide according to claim 2, wherein the member of the Tumor necrosis factor ligand superfamily is selected from the group consisting of LTA; TNF; LTβ; TNFSF4; TNFSF5; TNFSF6; TNFSF7; TNFSF8; TNFSF9; TNFSF10; TNFSF11; TNFSF12; TNFSF13; TNFSF13B; TNFSF14; TNFSF15; and TNFSF18.
4. A trimeric polypeptide according to claim 2, wherein the specific binding member is a polypeptide derived from a member of the Tumor necrosis factor receptor superfamily.
5. A trimeric polypeptide according to claim 2, wherein the member of the Tumor necrosis factor receptor superfamily is selected from the group consisting of TNFRSF1A, TNFRSF1B, LTBR, TNFRSF4, TNFRSF5, TNFRSF6, TNFRSF6B, TNFRSF7, TNFRSF8, TNFRSF9, TNFRSF10A, TNFRSF10B, TNFRSF10C, TNFRSF10D, TNFRSF11A, TNFRSF11B, TNFRSF12, TNFRSF12L, TNFRSF13B, TNFRSF13C, TNFRSF14, TNFRSF Fc14, NGFR, TNFRSF17, TNFRSF18, TNFRSF19, TNFRSF19L, TNFRSF21, TNFRSF22, and TNFRSF23.
6. A trimeric polypeptide according to claim 1, wherein the specific binding member is derived from TNFRSF1A (p55 TNF receptor).
7. A trimeric polypeptide according to claim 1, wherein the specific binding member is derived from TNFRSF1B (p75 TNF receptor).

8. A trimeric polypeptide according to claim 7, wherein the specific binding member is a polypeptide comprising an amino acid sequence selected from the group consisting of TNFRSF1B 1-235 (SEQ ID NO:76), TNFRSF1B 1-185 (SEQ ID NO:77), TNFRSF1B 1-163 (SEQ ID NO:78) and TNFRSF1B 1-142 (SEQ ID NO:79).

9. A trimeric polypeptide according to claim 7, wherein the specific binding member is a polypeptide comprising an amino acid sequence encoded by a DNA sequence selected from the group consisting of TNFRSF1B D1D2 (SEQ ID NO:13), TNFRSF1B D1D2, 1/6 (SEQ ID NO:15), TNFRSF1B D1D2 1/4 (SEQ ID NO:17), TNFRSF1B D1D2, 1/3 (SEQ ID NO:19), TNFRSF1B D1D2, 1/2 (SEQ ID NO:21), TNFRSF1B D1D4 (SEQ ID NO:23), TNFRSF1B D2 (SEQ ID NO:25), TNFRSF1B D2, 1/6 (SEQ ID NO:26), TNFRSF1B D2, 1/4 (SEQ ID NO:27), TNFRSF1B D2, 1/3 (SEQ ID NO:28), TNFRSF1B D2, 1/2 (SEQ ID NO:29) and TNFRSF1B D2D4 (SEQ ID NO:30).

10. A trimeric polypeptide according to claim 1, wherein the specific binding member is an antibody or antibody fragment.

11. A trimeric polypeptide according to claim 10, wherein the antibody or antibody fragment binds to human TNF (SEQ ID NO:80) in at least one region selected from the regions consisting of amino acid residues 1-18, 1-20, 1-26, 1-30, 12-22, 22-31, 22-40, 36-45, 49-97, 49-98, 56-79, 58-65, 69-97, 70-87, 76-90, 96-105, 105-128, 108-128, 110-127, 115-125, 117-128, 132-157, 135-155, 136-153, 138-149, 141-153 and 146-157.

12. A trimeric polypeptide according to claim 11, wherein the antibody or antibody fragment is selected from MAb 1 (ECACC 89080301), MAb 21 (ECACC 90012432), MAb 25 (ECACC 89121401), MAb 32 (ECACC 89080302), MAb 37 (ECACC 89080303), MAb 42 (ECACC 89080304), MAb 47 (ECACC 89121402), MAb 53 (ECACC 90012433) and MAb 54 (ECACC 89083103) or a fragment thereof.

13. A trimeric polypeptide according to claim 10, wherein the antibody is D2E7 or a fragment thereof.

14. A trimeric polypeptide according to claim 9, wherein the antibody is CDP 870 or a fragment thereof.
15. A trimeric polypeptide according to claim 1, wherein the specific binding member is a protein having the scaffold structure of C-type lectin-like domains (CTLD).
16. A trimeric polypeptide according to claim 15, wherein the specific binding member having the scaffold structure of C-type lectin-like domains is selected from the group consisting of TN3-2-B (SEQ ID NO:103), TN3-2-C (SEQ ID NO:104) and TN3-2-D (SEQ ID NO:105).
17. A trimeric polypeptide according to claim 1, wherein the trimerising domain is derived from tetranectin.
18. A trimeric polypeptide according to claim 17, wherein the trimerising domain derived from tetranectin comprises a sequence having at least 68% amino acid sequence identity with the sequence of SEQ ID NO:81.
19. A trimeric polypeptide according to claim 18, wherein the amino acid sequence identity is at least 75%, such as at least 87% including at least 92%.
20. A trimeric polypeptide according to claim 17, wherein the trimerising domain derived from tetranectin comprises the amino acid sequence SEQ ID NO:81.
21. A trimeric polypeptide according to claim 17, selected from the group consisting of TN-2-B (SEQ ID NO:106), TN-2-C (SEQ ID NO:108), TN-2-D (SEQ ID NO:107), and AD1D4-GSS-I10 (SEQ ID NO:109).
22. A trimeric polypeptide according to claim 1, further comprising a linker between the specific binding member and the trimerising domain.
23. A pharmaceutical composition comprising the trimeric polypeptide according to any of claims 1-22.

24. A method of treating a subject having a pathology mediated by a trimeric cytokine such as a tumor necrosis factor, comprising administering to said subject an effective amount of the trimeric polypeptide according to any of claims 1-22 or the composition according to claim 23.

25. A method according to claim 24 wherein the pathology mediated by tumor necrosis factor is selected from the group consisting of rheumatoid arthritis, psoriasis and Crohn's disease.

26. A method for the preparation of a trimeric polypeptide comprising three monomers, each of said monomers comprising a specific binding member capable of binding a trimeric polypeptide cytokine, and each of said monomers comprising a trimerising domain, said method comprising the steps of (i) culturing a host transformed with a vector encoding said trimeric polypeptide under such conditions that said trimeric polypeptide is expressed; and (ii) isolating said trimeric polypeptide.

27. A method according to claim 26, wherein said specific binding member comprises an amino acid sequence selected from the group consisting of TNFRSF1B 1-235 (SEQ ID NO:76), TNFRSF1B 1-185 (SEQ ID NO:77), TNFRSF1B 1-163 (SEQ ID NO:78) and TNFRSF1B 1-142 (SEQ ID NO:79).

28. A method according to claim 26, wherein the specific binding member is a polypeptide comprising an amino acid sequence encoded by a DNA sequence selected from the group consisting of TNFRSF1B D1D2 (SEQ ID NO:13), TNFRSF1B D1D2, 1/6 (SEQ ID NO:15), TNFRSF1B D1D2 1/4 (SEQ ID NO:17), TNFRSF1B D1D2, 1/3 (SEQ ID NO:19), TNFRSF1B D1D2, 1/2 (SEQ ID NO:21), TNFRSF1B D1D4 (SEQ ID NO:23), TNFRSF1B D2 (SEQ ID NO:25), TNFRSF1B D2, 1/6 (SEQ ID NO:26), TNFRSF1B D2, 1/4 (SEQ ID NO:27), TNFRSF1B D2, 1/3 (SEQ ID NO:28), TNFRSF1B D2, 1/2 (SEQ ID NO:29) and TNFRSF1B D2D4 (SEQ ID NO:30).

29. Use of a trimeric polypeptide according to any of claims 1-22.

30. Use of a trimeric polypeptide according to any of claims 1-22 for the preparation of a pharmaceutical composition.

31. An assay method for detecting a trimeric cytokine in a sample comprising (i) contacting said sample with a trimeric polypeptide according to claim 1, and (ii) detecting the binding of the trimeric polypeptide to the trimeric cytokine.